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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,725	02/28/2005	Hitoshi Okamoto	P26510	8296

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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/525,725	OKAMOTO ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 2, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 2, 2008 has been entered.

Election/Restrictions

In response to the Requirement for Restriction mailed July 3, 2006, Applicant had elected without traverse the invention of Group I, claims 1-8, drawn to vectors containing enhancer sequences from the Islet-1 gene, and cell lines containing said vectors.

Amendments

Applicant's response and amendments, filed October 2, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 9-13, and amended Claims 1-2 and 4-5.

Claims 1-8 are under consideration.

Specification

1. **The prior objection to the disclosure is withdrawn** in light of Applicant's amendment to the specification filed October 2, 2008 to clarify the identity of the nucleotides and their corresponding SEQ ID NO illustrated in Figures 14 and 17.

Claim Objections

2. **Claims 1 and 4-5 are objected to because of the following informalities**: The claims recite the phrase "as shown". It is the Examiner's position that the use of the phrase "as shown" renders the nucleotide sequences of SEQ ID NO:1-6 as an example only and may include reference to other, undisclosed, nucleotide sequences.

As-adverb

1. To the same extent or degree; equally: *The child sang as sweetly as a nightingale.*

2. For instance: *large carnivores, as the bear or lion.*

3. When taken into consideration in a specified relation or form: *this definition as distinguished from the second one.*

(answers.com/topic/as; last visited on March 15, 2007).

It would be remedial to remove "as", thereby improving the clarity of the claimed invention, i.e. subject-object agreement such as "*the* [emphasis added] nucleotide sequence...of SEQ ID NOs:1-4". See, for example, Claim 2(a).

3. **Claims 1-8 are objected to because of the following informalities**: The claims recite the phrase "according to". It is the Examiner's position that the use of the phrase "according to" renders the nucleotide sequences of SEQ ID NO:1-6 as an example only and may include reference to other, undisclosed, nucleotide sequences. It would be remedial to substitute "according to" for "of", thereby improving the clarity of the claimed invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 1-8 stand rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The instant claims, construed as discussed herein above, embrace an isolated regulatory element that is capable of enhancing gene expression efficiency in a motor or sensory neuron, wherein the structural characteristics of the claimed regulatory element are essentially unlimited.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the

genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

The Guidelines further state, "[s]atisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the genus in view of the species disclosed" (Id. at 1106, column 3).

In the instant case, the application discloses 6 sequences, which, based on the discussion in Examples 1-4 are presumed to be genomic DNA upstream of the 5' upstream genomic neuronal-specific enhancer sequence for the zebrafish, human, mouse, and pufferfish Islet-1 gene. However, there is no demonstration in the disclosure that the sequences set forth as SEQ ID NO: 1-6 as defined by the broad claims 1, 2, 4 and 5 are sufficient to drive transcription in any or all motor or sensory neuronal cells as recited in the claim. Claims 1, 2, 4 and 5 are broad and read on any sequence capable of eliciting the same enhancing capabilities of the SEQ IDs listed in the claims by deletion, substitution or addition of one to thirty nucleotides. Is the limitation directed at limiting the changes to 30 nucleotides, such that only individual nucleotides a changed? Or can multiple regions be deleted, as long as the individual region is no longer than 30 nucleotides? The claimed nucleotide sequences are hundreds of base pairs long. There is no teaching of which thirty base pairs are to be changed, or how to determine which nucleotides should be altered. The deletion or addition or substitution of even a single nucleotide has the potential to disrupt the enhancer function of the claimed SEQ ID NO. Therefore, it is not clear that the claimed alterations of the sequences set forth in the sequence listing in the claims are actually species of the invention.

Even if one is to assume, *arguendo*, that the functional properties recited in the instant claims are inherent to the nucleic acids set forth as SEQ ID NO: 1-6, these species are not representative of the broad genus claimed because they clearly do not convey the necessary common attributes or features of essentially any nucleic acid having the recited function.

Furthermore, with regard to the "relevant identifying characteristics" of the claimed invention, the specification provides no disclosure of the structural features that define the function recited in the claims. As stated in MPEP 2163(I)(A), a biomolecules sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes. Thus, applications that seek to claim biological molecules having a defined function and broadly divergent structure must disclose a correlation between that function and a corresponding structure. Although example 2 identifies high homology between SEQ ID NO: 1-4 in base pairs 235-560, 204-528, 206-530 and 211-555 respectively there is no evidence that these specific sequences are sufficient to define a genus wherein these sequences comprises a "deletion, substitution or addition of one to thirty nucleotides" is capable of driving transcription in any or all motor or sensory neuronal cells as presently claimed.

Therefore, the application also fails to provide the relevant identifying characteristics of the claimed invention.

An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property (i.e., it is capable of driving transcription in a neuronal- specific manner) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the Applicant was in possession of the claimed invention because it does not provide adequate written description for the broad class of a nucleotide sequence of SEQ ID NO: 1-6 in which deletion, substitution or addition of one to thirty nucleotides is capable of driving transcription in a motor or sensory neuron beyond the scope of a nucleic acid selected from the group consisting of a nucleic acid consisting of SEQ ID NO: 1-6. Therefore, the claims are properly rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Response to Arguments

Applicant argues that the claimed subject matter encompasses nucleic acid sequences at least 95% homologous to the reference SEQ ID NO and which have a particular function, specifically improving gene expression efficiency in motor neurons (SEQ ID NOs: 1-4) and sensory and/or motor neurons (SEQ ID Nos:5-6). Applicants submit that the specification describe the common *function* of the claimed genus of sequences. Furthermore, the specification describes the common *structure* of the claimed genus of sequences by describing the regions of homology in SEQ ID NOS. 1-6, and the location of these homologous regions within SEQ ID NOS. 1-6.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant's own post-filing work (Uemura et al, Dev. Biol. 278:587-606, 2005) teaches that the sensory neuron-specific activity of zebrafish CREST2 (SS enhancer element of SEQ ID NO:5) depends on a sequences that is **not conserved** in evolution, and human CREST2 (SEQ ID NO:6) does not have this activity (pg 588, col. 2, ¶1). hCREST2 does not have the sensory neuron-specific enhancer activity (Fig. 4B) show that both evolutionarily conserved and nonconserved

regions of zCREST2 are necessary for the sensory neuron-specific activity in zebrafish (pg 599, col. 1). Thus, despite the presence of conserved nucleotides between zebrafish and humans, illustrated in Figure 17 of the instant application, indicating the common core structure argued by Applicant, Applicant's own post-filing work teaches that this common structure is **insufficient** for the instantly claimed function. Furthermore, **deletion** of 100 nucleotides 5' to CREST2 (first 100 nucleotides of SEQ ID NO:5), yet retaining those nucleotides illustrated in Figure 17 of the instant application as the common core structure, **abolished** enhancer **activity** (Uemura et al, Figures 5B and 5C). Again, Applicant's own work teaches that the instantly disclosed common core structure is insufficient to achieve the claimed functional property.

Similarly, Uemura et al teach that a **substitution of four nucleotides** in CREST1 (enhancer element of SEQ ID NOs:1-4) completely **abolished** enhancer **activity** (pg 596-597, Figure 5A and legend). Sequence comparison and TRANSFAC analysis revealed that there are putative recognition motifs for **multiple transcription factors** in evolutionarily conserved region of CREST1 (pg 602, col. 1, ¶2). Thus, nucleotide insertions, deletions or substitutions may abrogate the binding of one or more transcription factors necessary for the instantly claimed activity, as demonstrated by Applicant's above mutation.

Applicant is respectfully reminded that the instant specification discloses **no examples** of mutagenesis of the claimed enhancers to suggest that such alterations will retain enhancer properties. The substantive issue is that the claims reasonably embrace an enormous genus of sequence permutations in those nucleic acid sequences, SEQ ID NO:1-4 and SEQ ID NO:5-6, respectively, disclosed to have a common structure and/or function. However, if a plurality of nucleotides are allowed to be mutated in SEQ ID NO:1-4 and SEQ ID NO:5-6, then the species within a given SEQ ID NO and between the recited SEQ ID NO's no longer share a common structure, and Applicant's own work (Uemura) teaches that the instantly disclosed common structure is **insufficient** to fulfill the recited functions. The specification does not disclose what polymorphic variants of the preferred SEQ ID NO subdomains share a common nucleotide sequence **necessary and sufficient** for the functional property. Thus, Applicant is claiming an enormous genus of polynucleotides wherein the non-functional embodiments are structurally indistinguishable from *possibly* functional embodiments. The specification provides no guidance as to which nucleotides may be changed without altering the function of SEQ ID NOs:1-6.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. **Claims 6-8 are rejected under 35 U.S.C. 102(b)** as being anticipated by Higashijima et al (J. Neurosci. 20(1):206-218, 2000; *of record in IDS).

The claims, as written, are drawn to a vector comprising the enhancer of claim 1, further comprising a promoter and a gene comprising a coding region. As such, the breadth of the claim reasonably embraces a genomic BAC vector clone comprising said structural elements.

Higashijima et al teach a BAC vector clone, N21 of approximately 91 kilobases in length, comprising a zebrafish genomic nucleic acid sequence comprising the enhancer of claim 1, specifically SEQ ID NO:1, said BAC vector further comprising a promoter and the *islet-1* gene comprising a coding region (pg 207, Figure 1).

Higashijima et al do not teach the nucleotide sequence of SEQ ID NO:1. However, the instant specification discloses that "SEQ ID NO: 1 is contained in a region located approximately 10 kbp downstream of the transcription initiation site of the Islet-1 gene of the zebrafish genome." (pg 7, lines 7-9) Thus, absent evidence to the contrary, SEQ ID NO:1 is inherently present in the NS1 BAC clone of Higashijima et al that comprises the zebrafish *Islet-1* gene and at least 70 kilobases (kbp) downstream of the transcription initiation site of the Islet-1 gene of the zebrafish genome (pg 207, Figure 1).

Higashijima et al do not explicitly teach a transgenic cell line comprising BAC N21. However, the breadth of "transgenic cell" reasonably embraces bacterial cells routinely used for molecular cloning, and those of ordinary skill in the art recognize that Bacterial Artificial Chromosomes (BAC) clones are propagated in bacterial cells. Thus, a transgenic cell line comprising N21 is inherently taught by Higashijima et al.

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633